## REMARKS

Claims 1 through 3, 6 through 12 and 14 through 18 are pending in the application.

Claim 1 has been amended to emphasize advantageous transdermal therapeutic systems in which the first active ingredient-containing polymer layer is disposed on the backing layer and the second active ingredient-containing polymer layer is disposed on the first active ingredient-containing polymer layer. Support for this amendment can be found in the Application as filed, for example on Page 12, lines 15 through 29 (Example 2).

Claim 1 has also been amended to emphasize advantageous transdermal therapeutic systems in which pramipexol is present in the first active ingredient-containing polymer layer in a proportion of between 25 to less than 75 % by weight and in the second active ingredient-containing polymer layer in a proportion of between 2 and 10 % by weight. Support for this amendment can be found in the Application as filed, for example on Page 12, lines 3 through 13 (Example 2) in conjunction with Page 10, lines 8 through 13 and Page 11, lines 17 through 20 and Page 8, lines 13 through 18.

Claim 1 has additionally been amended to emphasize advantageous transdermal therapeutic systems in which the second active ingredient-containing polymer layer includes carboxyl group-free polyacrylate pressure-sensitive adhesive. Support for this amendment can be found in the Application as filed, for example on Page 12, lines 3 through 13 (Example 2) in combination with Page 8, lines 7 through 13.

Claim 14 has been amended to conform to Claim 1 as-amended, and reflects advantageous transdermal therapeutic systems in which the pramipexol is present in the first active ingredient-containing polymer layer in a proportion of between 25 and 40 % by weight. Support for this amendment can be found in the Application as filed, for example on Page 10, lines 8 through 13.

Claim 16 has been amended to reflect advantageous transdermal therapeutic systems in which the pressure-sensitive adhesive does not comprise water or an aqueous dispersion. Support for this amendment can be found in the Application as filed, for example on Page 8, lines 18 through 23.

Claim 18 has been amended to reflect advantageous transdermal therapeutic systems that do not include a pressure sensitive top plaster. Support for this amendment can be found in the Application as filed, for example on Page 5, lines 10 through 15.

Applicants respectfully submit that this response does not raise new issues, but merely places the above-referenced application either in condition for allowance, or alternatively, in better form for appeal. Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

*The Claimed Invention is Patentable*
*in Light of the Art of Record*

Claims 1 through 3, 6 through 12, and 14 through 18 stand rejected over WIPO Published Application WO 03/015779, whose United States Equivalent is United States Publication 2004/0247656, which has subsequently matured into United States Patent No. 7,344,733 (US 733) to Beier et al. in view of United States Patent No. 5,112,842 (US 842) to Zierenberg et al. and WIPO publication WO 96/39136 (WO 136) to Patel et al. Claim 16 stands rejected over the foregoing references and further in light of United States Patent No. 5,238,944 (US 944) to Wick et al. and United States Patent No. 6,365,178 (US 178) to Venkateshwaran.

It may be useful to consider the invention as recited in the claims before addressing the merits of the rejection.

Transdermal therapeutic systems ("TTSs") provide a promising option for the continuous delivery of active ingredients over a prolonged period of time. TTSs deliver an active ingredient continuously and in a controlled manner to the patient's skin. After passing through the various layers of skin, the active pharmaceutical ingredient is taken up by the underlying blood vessels.

Unfortunately, the delivery of a sufficient quantity of active ingredients in a controlled manner over a prolonged time period via mass diffusion, initially through the TTS and subsequently the dermis, is quite challenging. In particular, a significant quantity of the active ingredient must be incorporated into the TTS to provide a sufficient level of diffusion over an extended period of time, such the conventional period of one to three days.

Many polymers capable of sustaining more elevated loadings of active ingredients do not possess adhesive properties. This is problematic because the TTS must adhere securely to the patient's skin in order to deliver the active ingredient. As discussed in US 733, such non-adhesive polymers may also induce degradation within active ingredients, particularly pramipexole.

Adhesive polymers incorporating active ingredient may be used; however, active ingredients can be detrimental to the resulting adhesive polymer properties, with such detriment expected to be exaggerated at higher active ingredient loadings. Many polymers, such as pressure sensitive polymers, are also generally understood to require excipients, such as penetration enhancers, to effectively deliver drugs transdermally, as evidenced in cited US 733 incorporating Copherol® to aid pramipexol in penetrating the skin from a polyacrylate matrix.

Applicants have also determined that conventional single-layered TTSs formed from pressure sensitive adhesive matrices exhibit a significant lag time before delivering an adequate pramipexol flux. A single layered TTS incorporating 10 % by weight pramipexol takes approximately 32 hours to develop a flux rate greater than 5 $\mu g/cm^2$ hr, for example, as illustrated in Figure 1 of the Application-as-filed.

Quite unexpectedly, Applicants have determined that TTSs incorporating two active-ingredient containing layers formed from pressure sensitive adhesive addresses this lag time, providing an adequate pramipexol flux within 24 hours of application. For example, a two layered TTS incorporating only 3 % by weight pramipexol in the skin side layer and 40 % by weight pramipexol in the outermost layer takes less than 24 hours to develop a flux rate greater than 5 $\mu g/cm^2$ hr, as illustrated in Figure 2 of the Application-as-filed. Such provision of a significantly higher flux rate at the 24 hour mark by a two layered TTS initially providing less active ingredient immediately adjacent the skin in comparison to a single layered TTS (i.e. 2 wt % versus 10 wt %) is altogether unexpected, to say the least.

In fact, such incorporation of two pramipexol-containing polymer layers, e.g. an outermost layer formed from pressure sensitve adhesive containing a significantly higher loading of pramipexol in addition to a second pressure sensitive adhesive layer containing a much more moderate loading of pramipexol directly adjacent to the patient's skin, provides a significantly higher flux rate at both 24 hours and 72 hours in comparison to a comparable TTS containing a moderate amount of pramipexol within a single layer. In that regard, the Examiner's attention is kindly directed to the Application-as-filed, particularly to Page 12, lines 3 through 33 and Figures 1 and 2. Although not wishing to be bound by theory, Applicants can only surmise that the concentration gradient arising within Working Example 2 resulted in a highly beneficial and altogether unexpected increase in the mass diffusion of pramipexol.

In contrast to the opinion urged within the outstanding Office Action on Page 12, last partial paragraph, the advantages of Formulation 2 versus Formulation 1 are readily evidenced in the Application-as-filed by a comparison of Figures 1 and 2, illustrating the respective flux rates of Formulation 1 and Formulation 2 over a 72 hour period. The inventive two-active-ingredient-layered TTSs provided a flux rate of greater than 5 $\mu g/cm^2$ hr at the 24 hour mark and a flux rate approaching 18 $\mu g/cm^2$ hr at the 72 hour mark, as shown in Figure 2 of the Application-as-filed. In contrast, a comparable single-active-ingredient-layered TTS provided a flux rate of less than 1 $\mu g/cm^2$ hr at the 24 hour mark and a flux rate of about 14 $\mu g/cm^2$ hr at the 72 hour mark, as

shown in Figure 1 of the Application-as-filed. The elevated flux rates provided by the claimed invention translates into a much quicker and more prolonged efficacy for the patient.

Accordingly, the claims are directed to advantageous transdermal therapeutic systems for continuous administration of pramipexol that include both first and second pramipexol-containing polymer layers formed from pressure-sensitive adhesive polymer based on carboxyl group-free polyacrylates, in which the first pramipexol-containing polymer layer, disposed adjacent the backing layer, includes pramipexol in an elevated proportion of between 25 up to 75 % by weight and the second pramipexol-containing layer, disposed toward the skin, includes pramipexol in a more modest proportion of 2 to 10% by weight, with the resulting TTS providing a flux rate of greater than 5 $\mu g/cm^2$ after only 24 hours after application, with such beneficial flux rate continuing for up to 72 hours after administration, as reflected in Claim 1 as-amended.

In advantageous embodiments, the inventive TTSs provide such elevated and prolonged flux rates in the absence of excipients or penetration-promoters, and further without resort to an additional top plaster, as recited in Claim 18 as-amended.

The cited references do not teach or suggest the claimed invention.

Applicants respectfully reiterate that US 733 is generally directed to directed to single layer TTSs providing improved shelf stability that include a maximum of 15 % by weight active ingredient. (Col. 2, line 66 - Col. 3, line 2 and Col. 2, lines 19 - 20). US 733 provides a generic laundry list of suitable pressure sensitive adhesives, including polyurethane. (Col. 3, lines 23 – 26). US 733 notes acrylic acid and methacrylic acid as suitable monomers within its matrix polymer. (Col. 3, lines 50 – 52). US 733 merely generically notes that its systems may include one or more matrix layers. (Col. 2, lines 40 – 45). US 733 notes that permeation enhancers may be included "where applicable." (Col. 2, lines 40 – 45). The working examples of US 733 expressly teach the incorporation of permeation enhancer, i.e. Copherol®, in conjunction with acrylic-based matrix layers; however. (Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)). The working examples of US 733 further teach the incorporation of 2.5 to 3 weight % active

ingredient within a single layer of acrylic-based matrix. (Col. 4, line 43 – Col. 6, line 27 (Exs. 1 - 3)).

US 733 thus does not teach or suggest the claimed invention.

As indicated by the Examiner, US 733 does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration.

Nor does US 733, generically noting that its devices may include more than one matrix layer, teach or suggest advantageous TTSs including a first active ingredient-containing polymer layer and a second active ingredient layer in which the first layer contains significantly greater amount of active ingredient than the second layer, as further recited in Claim 1 as-amended.

US 733, generically noting any of a laundry list of adhesives and a maximum of 15% active ingredient, further does not teach or suggest a first active ingredient-containing polymer layer formed from carboxyl group-free polyacrylates including from 25 up to 75 % by weight pramipexol, as additionally recited in Claim 1 as-amended.

And US 733 most certainly does not teach or suggest such advantageous transdermal therapeutic systems further including a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol, as recited in Claim 1 as-amended.

US 733, expressly teaching penetration enhancer with polyacrylate matrices, also fails to teach or suggest advantageous TTSs in which the first and second active ingredient-containing polymer layer is formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates which have a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 to 72 hours after administration in the absence of excipients or penetration-promoters, as recited in Claim 18. Applicants respectfully reiterate that US 733 instead teaches away from such

advantageous embodiments by expressly teaching the use of permeation enhancers, i.e. Copherol®, in conjunction with a polyacrylate matrix layer.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 733, considered either alone or in any combination with the remaining art of record.

The secondary references do not overcome the deficiencies in US 733.

US 842 is likewise directed to single-active-ingredient-layer TTSs that further include a covering plaster which "secure[s] the system to the skin." (US 842, Col. 2, lines 11 – 15). US 842 broadly notes that its active ingredient layer may be formed from "emulsion polymerized polyacrylate," preferably Eudragit® NE 30 D (US 842, Col. 1, line 64 – Col. 2, line 2 and Col. 2, lines 18 – 20). As noted in the Application as-filed on Page 3, line 35 through Page 4, line 1, Eudragit® NE 30 D is not a pressure sensitive adhesive. Consequently, a covering plaster is used to secure the system to the skin, as noted by the Examiner. (US 842, Col. 2, lines 11 – 15). The working examples of US 842 include 9 wt % active substance within a single layer. (US 842, Col. 2, lines 53 – 62). US 842 curiously provides concentration data beginning on the 3rd day and ending on the 4th day following application. (US 842, Col. 3, lines 2 – 12). In vitro investigations on samples of the TTSs indicate that about 70 % of the amount of active ingredient had been delivered after only 4 days and that only about a further 10% of the amount of active ingredient originally present in the reservoir can be released in the subsequent three days. (US 842, Figure 1, as interpreted in the Application-as-filed on Page 4, lines 9 – 14). The primary reference, US 733, further teaches that pramipexole decomposes "very rapidly" within the polyacrylate of US 842 and that the active ingredient would additionally crystallise out. (US 773, Col. 1, lines 57 – 65).

US 842, solely directed to single-active-ingredient-layer TTSs, does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ hr at 24 hours after administration, as recited in the claimed invention. Applicants

respectfully reiterate that single-layered-active-ingredient TTSs would instead be expected to perform poorly at the 24 hour mark, as indicated in Figure 1 of the Application-as-filed.

Nor does US 842 teach or suggest advantageous TTSs including first and second active ingredient-containing polymer layers, as further recited in Claim 1.

US 842, teaching only a non-adhesive matrix layer, further does not teach or suggest such polymer layers formed from carboxyl group-free polyacrylate pressure sensitive adhesive, as additionally recited in Claim 1 as-amended.

And US 842, teaching a maximum of 30 % active ingredient within its matrices, most certainly does not teach or suggest such advantageous transdermal therapeutic systems including a first active ingredient-containing polymer layer including up to 75 % pramipexol, and particularly not in combination with a second active ingredient-containing polymer layer comprising between 2 and 10% pramipexol, as recited in Claim 1 as-amended.

US 842, expressly teaching the use of a top plaster in conjunction with its non-adhesive matrix, also fails to teach or suggest such advantageous TTSs which include no additional pressure sensitive top plaster, as additionally recited in Claim 18 as-amended.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 842, considered either alone or in any combination with the remaining art of record.

WO 136 is merely directed to the use of ropinirole in free base form as an active ingredient in either membrane-based or maxtrix-based transdermal devices. (Page 1, line 34 – Page 2, line 5 and Page 2, lines 15 - 21). The working examples of WO 136 include a single drug-containing layer formed from either a saline/propylene glycol "vehicle" within the membrane-based TTS or a hydrogel within the matrix-based TTS. (Page 4, lines 14 – 36). The hydrogel of WO 136 is formed from polyvinyl alcohol ("PVA") and polyvinylpyrrolidone ("PVP"). (Page 4, lines 33 – 34). The hydrogel further includes glycerin as an excipient. (Page

4, line 34). The working examples include either a silicone adhesive or undisclosed adhesive. (Page 4, lines 14 – 36).

WO 136 expressly teaches that its unit doses are intended for once-a-day application. (Page 3, lines 24 – 26). WO 136 merely provides extended penetration data based upon the percutaneous penetration of the saturated saline or saline/propylene glycol vehicle alone. (Page 5, lines 1 – 21). In contrast to the opinion urged within the Office Action on Page 7, first partial paragraph, WO 136 does not teach or suggest that its TTSs provide such extended release, but instead tests suspensions of ropinirole to determine its "relative potential" in transdermal systems. (Page 5, lines 3 – 5). WO 136 goes on to note that, based on its initial solution study, a sufficient quantity of ropinirole free based was found to penetrate the skin for a 24 hour period and a patch delivering a sufficient quantity of ropinirole could "potentially" be formed. (Page 6, lines 7 – 9). Applicants respectfully submit that working patches incorporating the tested vehicle would further include a membrane, as taught in Example 1 of WO 136.

Applicants further respectfully make of record that, regardless of its use in treating Parkinson's disease, the chemical structure of ropinirole is altogether different from that of pramipexole. Furthermore, the saline/propylene glycol "vehicle" of WO 136 is likewise altogether different from the claimed pressure sensitive adhesives. Hence the diffusional properties of ropinirole within a saline/propylene glycol vehicle can not be imputed to pramipexole within pressure sensitive adhesive, and statements to the contrary are merely conjecture. More particularly, the diffusional properties of ropinorole within either the tested saline/propylene glycol solution or the prospective polyvinyl alcohol/ polyvinylpyrrolidone hyrogel/silicone adhesive system can not be imputed to the inventive transdermal systems incorporating pramipexole within carboxyl group-free polyacrylate pressure-sensitive adhesive layers.

Applicants thus respectfully reiterate that WO 136 does not teach transdermal therapeutic systems in which the active ingredient pramipexol has a flux rate greater than 5 $\mu g/cm^2$ h at 72 hours after administration, as recited in the claimed invention. As noted above, WO 136 is

directed to TTSs intended for daily application and merely provides extended penetration data based upon the percutaneous penetration of ropinirole from saline or saline/propylene glycol solutions, not its PVA/PVP hyrdogel matrices or any resulting TTS.

Nor does WO 136, solely directed to single-layered-active-ingredient TTSs, teach or suggest advantageous TTSs including first and second active ingredient-containing polymer layers, much less such layers formed from pressure-sensitive adhesive, and most certainly not carboxyl group-free polyacrylate pressure sensitive adhesive, as recited in Claim 1. WO 136 instead expressly teaches a single active ingredient layer formed from either a polyvinyl alcohol/polyvinylpyrrolidone matrix or a saline/propylene glycol dispersion.

And WO 136 most certainly does not teach or suggest that advantageous transdermal therapeutic systems for continuous administration of pramipexol including a first active ingredient-containing polymer layer comprising between 25 to less than 75 % by weight pramipexol and a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol would result in a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after TTS administration, as recited in Claim 1 as-amended.

WO 136, expressly teaching a glycerin excipient within its matrix-based TTSs, likewise fails to teach or suggest transdermal therapeutic systems formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that provide such advantageous flux rates in the absence of excipients, as recited in Claim 18.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of WO 136, considered either alone or in any combination with the remaining art of record.

Applicants respectfully reiterate that here would have been no motivation to have combined US 733, US 842 and WO 136. Applicants respectfully submit that merely because the references can be combined is not enough, there must still be a suggestion. MPEP 2143.01

However, even if Applicants had combined US 733, US 842 and WO 136 (which they did not), the claimed invention would not have resulted.

Applicants respectfully reiterate that the combination particularly does not teach or suggest that transdermal therapeutic systems incorporating two pramipexol-containing layers would result in a pramipexol flux rate greater than 5 $\mu g/cm^2$ h at 24 to 72 hours after administration, as recited in the claimed invention.

And the combination most certainly does not teach or suggest that advantageous transdermal therapeutic systems including an outermost active ingredient-containing polymer layer comprising between 25 to less than 75 % by weight pramipexol and a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol, in which the outermost and second active ingredient-containing polymer layers are formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates would result in transdermal therapeutic systems releasing pramipexol at a flux rate greater than 5 $\mu g/cm^2$ h from 24 to 72 hours after administration. As indicated by the Examiner in the outstanding Office Action on Page 7, last partial paragraph, US 733 at best suggests multiple active ingredient layers including from 2 to 15 % active ingredient. US 842 and WO 136, both silent as to multiple active-ingredient layers, do not cure the deficiency in US 733.

And the combination can not teach or suggest transdermal therapeutic systems incorporating first and second active ingredient-containing polymer layers formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that provide such advantageous flux rates in the absence of excipients or penetration-promoters and further without a top plaster, as recited in Claim 18 as-amended. US 733 expressly teaches the incorporation of a penetration promoter in conjunction with polyacrylate pressure sensitive adhesives. WO 136 expressly teaches the use of a glycerin excipient within its matrix-based TTSs. US 842 expressly teaches the use of top plasters within its TTSs.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of each of US 733, US 842 and WO 136, considered either alone or in any combination with the remaining art of record.

Applicants respectfully reiterate that the Office Action's urging on Page 8, last partial paragraph, comparing the release rate of scopolamine, fentanyl and estrogen-progestin patches with rates attainable for pramipexol TTSs is pure conjecture. Applicants more particularly respectfully reiterate that the chemical structures of scopolamine, fentanyl and estrogen-progestin each differs significantly from the claimed pramipexol, and that the physical properties (inter alia the solubilities, mass transport properties and efficacies) of such widely differing compounds thus can not be imputed to the recited pramipexol. Applicants respectfully reiterate that the Office Action is instead indulging in impermissible hindsight analysis by merely picking and choosing elements from the prior art while using the instant specification as the guide for that selection process.

Claim 16 is likewise patentable in further view of US 944 and US 178.

US 944 is directed to formulations for the topical or transdermal delivery of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine using isostearic and/or oleic fatty acid. (Col. 1, lines 49 – 63 and Col. 2, lines 1 - 4). The fatty acid may be included in amounts of up to 45 % by weight. (Col. 3, lines 49 – 52). The 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine may be present in amounts of up to 9 % by weight. (Col. 3, lines 43 – 46). US 944 indicates that suitable adhesives include 4 to 9 % acrylic acid or methacrylic acid reinforcing monomer, as noted by the Examiner in the outstanding Office Action on Page 9, last partial paragraph. (Col. 6, lines 23 – 24 and lines 33 - 34). US 944 is merely directed to single-layered transdermal devices. (Col. 16, lines 45 – 65).

Applicants respectfully submit that US 944 does not teach or suggest the claimed invention.

US 944, solely directed to 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine formulations, does not teach or suggest the inventive transdermal therapeutic systems incorporating pramipexol.

Nor does US 944, directed to conventional single layer TTSs including up to 9 % active ingredient, teach or suggest such transdermal therapeutic systems including first and second active ingredient-containing polymer layers, much less such layers in which the first active ingredient-containing layer incorporates from 25 to less than 75 % by weight pramipexol and the second active ingredient-containing layer incorporates up to 10 % by weight pramipexol.

And US 944, expressly teaching 4 to 9 % acrylic acid or methacrylic acid reinforcing monomer, most certainly does not teach or suggest the inventive transdermal therapeutic systems in which the active ingredient-containing layers are formed from carboxyl group-free polyacrylates, as further recited in Claim 1.

US 944, directed to single layered TTSs incorporating 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, likewise fails to teach or suggest such transdermal therapeutic system that release the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration.

Accordingly, Applicants respectfully submit that US 944 does not teach or suggest Claim 16, considered either alone or in any combination with the remaining art of record.

US 178 is generally directed to single-layered TTSs incorporating hydrophilic salts of hydrophobic drugs within aqueous dispersions of pressure sensitive adhesive polymers. (Col. 3, lines 55 – 60 and Col. 4, lines 1 - 15). Exemplary hydrophobic drugs include albuterol sulphate, ketorolactromethamine. (Col. 4, lines 20 – 25). US 178 clearly differentiates between solvent-solublized adhesives and water-soluble adhesives. (Col. 6, lines 32 – 37). US 178 emphasizes the importance of water-based adhesives to its invention, noting that "the subject of the present invention" is the addition of a hydrophilic salt of a hydrophobic drug directed to a water-based

adhesive, with subsequent evaporation of the water. (Col. 8, lines 11 – 18). The working examples of US 178 indicate that hydrophilic drug salts form crystals within solvent based adhesives, even after repeated attempts. (Col. 11, lines 10 – 21). The working examples of US 178 incorporate 5 % active ingredient. (Col. 11, lines 6 – 9).

Applicants respectfully submit that US 178 does not teach or suggest the claimed invention.

US 178, directed to formulations incorporating albuterol sulphate and the like, does not teach or suggest the inventive transdermal therapeutic systems incorporating pramipexol.

Nor does US 178, directed to conventional single layer TTSs including 5 % active ingredient, teach or suggest such transdermal therapeutic systems including first and second active ingredient-containing polymer layers, much less such layers in which the first active ingredient-containing layer incorporates from 25 to less than 75 % by weight pramipexol and the second active ingredient-containing layer incorporates up to 10 % by weight pramipexol.

US 178 thus likewise fails to teach or suggest such transdermal therapeutic system that release the active ingredient pramipexol with a flux rate greater than 5 $\mu g/cm^2$ hr over the period between 24 hours after administration to 72 hours after administration.

And US 178, requiring a water based adhesive, most certainly does not teach or suggest such transdermal therapeutic systems in which the pressure-sensitive adhesive does not comprise water or an aqueous dispersion, as recited in Claim 16 as-amended.

Accordingly, Applicants respectfully submit that US 178 similarly does not teach or suggest Claim 16, considered either alone or in any combination with the remaining art of record.

Applicants respectfully submit that there likewise would have been no motivation to have combined US 733, US 842, WO 136 and US 944 or US 178. However, even if Applicants had combined the foregoing references (which they did not), the claimed invention would not have resulted.

Applicants respectfully reiterate that the combination particularly does not teach or suggest that transdermal therapeutic systems incorporating two pramipexol-containing layers would result in a pramipexol flux rate greater than 5 $\mu g/cm^2$ h at 24 to 72 hours after administration, as recited in the claimed invention.

And the combination most certainly does not teach or suggest that advantageous transdermal therapeutic systems including an outermost active ingredient-containing polymer layer comprising between 25 to less than 75 % by weight pramipexol and a second active ingredient-containing polymer layer comprising between 2 and 10 % by weight pramipexol, in which the outermost and second active ingredient-containing polymer layers are formed from pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates would result in transdermal therapeutic systems releasing pramipexol at a flux rate greater than 5 $\mu g/cm^2$ h from 24 to 72 hours after administration. As indicated by the Examiner in the outstanding Office Action on Page 7, last partial paragraph, US 733 at best suggests multiple active ingredient layers including from 2 to 15 % active ingredient. US 842, WO 136, US 994 and US 178, each silent as to multiple active-ingredient layers, do not cure the deficiency in US 733. US 994 further expressly teaches the incorporation of carboxyl-group containing adhesive, which Applicants have determined to be unsuitable for production.

The combination further does not teach or suggest such transdermal therapeutic systems in which the pressure-sensitive adhesive does not comprise water or an aqueous dispersion, as recited in Claim 16 as-amended. As noted above, the impetus of US 178 is instead the incorporation of an active ingredient salt in water based adhesive.

Accordingly, Applicants respectfully submit that Claim 16 is likewise patentable in light of each of US 733, US 842, WO 136, US 994 and US 178considered either alone or in any combination with the remaining art of record.

## CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1 through 3, 6 through 12 and 14 through 18 are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that extensions of time or fees are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time and/or fees are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required is hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

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